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(54) Azolylmethyloxiranes, Their Preparation and Their Use as Drugs

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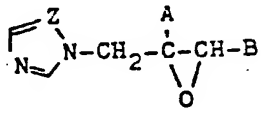
Azolylmethyloxiranes, their preparation and their use as drugs

The present invention relates to novel azole compounds, processes for their preparation, therapeutic agents which contain these compounds and can be used as antimycotics, and their use in the treatment of disorders.

A large number of antimycotic agents, eg. miconazole (German Laid-Open Application DOS 1,940,388), is known. Their actions are not always satisfactory (Chemotherapy 22, (1976), 1; Dtsch. Apoth. Ztg. 118 (1978), 1,269; and Z. Hautkr. 56 (1981), 1,109). It has also been disclosed that azole compounds, eg. azolylmethylcarbinols or azolylmethyl ketones (German Laid-Open Application DOS 2,431,407 and French Patent 2,249,616), can be used as fungicides.

It is an object of the present invention to provide novel and more active antimycotics and fungicides.

We have found that this object is achieved, and that compounds of the formula I



(I),

where A and B are identical or different and are each alkyl of 1 to 4 carbon atoms, naphthyl, biphenyl or phenyl, and the phenyl radical can be substituted by halogen, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, phenoxy or phenylsulfonyl, and Z is CH or a nitrogen atom,

and their physiologically or pharmaceutically acceptable or plant-tolerated addition salts with acids, possess good antimicrobial, in particular antimycotic, properties.

The novel compounds of the formula I contain chiral centers, and are obtained in general in the form of racemates or as diastereomer mixtures of the erythro and threo forms. The erythro and threo diastereomers of the novel compounds can be separated, for example, by utilizing the difference in their solubilities, or by column chromatography, and can be isolated in pure form. Individual enantiomers can be obtained from such pure diastereomer pairs by a conventional method. Both the pure diastereomers or enantiomers and the mixtures thereof which are obtained in the synthesis can be used as antimicrobial agents.

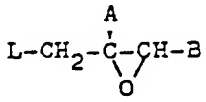
A and B are each, for example, methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, isobutyl, tert.-butyl, naphth-1-yl, naphth-2-yl, p-biphenyl, phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-bromophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-chloro-4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 2,4-dimethoxyphenyl, 3,4-dimethoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-tert.-butoxyphenyl, 4-methylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-tert.-butylphenyl, 4-phenoxyphenyl, 3-phenoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl or 4-phenylsulfonylphenyl, preferably methyl, tert.-butyl, phenyl, 4-chlorophenyl, 4-bromophenyl, 2,4-dichlorophenyl or

4-tert.-butylphenyl.

Acids which are preferably used for the formation of physiologically tolerated salts include hydrohalic acids, eg. hydrochloric acid and hydrobromic acid, in particular hydrochloric acid, with which the novel compounds form salts which crystallize particularly readily; further examples are phosphoric acid, nitric acid, sulfuric acid, monofunctional and bifunctional carboxylic acids and hydroxycarboxylic acids, eg. acetic acid, oxalic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid, salicylic acid, sorbic acid and lactic acid, and sulfonic acids, eg. p-toluenesulfonic acid and naphthalene-1,5-disulfonic acid.

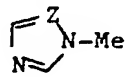
The novel compounds of the formula I can be prepared by a process wherein

a) a compound of the formula II



(II),

where A and B have the above meanings and L is a leaving group which can undergo nucleophilic substitution, is reacted with a compound of the formula III

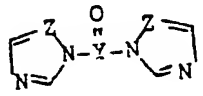


(III),

where Me is hydrogen or a metal atom and Z is CH or a

nitrogen atom, or

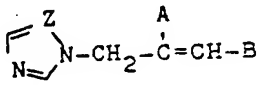
b) a compound of the formula II, where A and B have the above meanings and L is hydroxyl, is reacted with a compound of the formula IV



(IV),

where Z has the above meanings and Y is carbon or sulfur, or

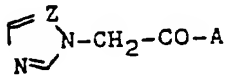
c) a compound of the formula V



(V),

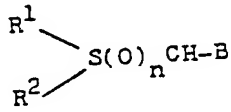
where Z, A and B have the above meanings, is epoxidized, or

d) a compound of the formula VI



(VI),

where Z and A have the above meanings, is reacted with a compound of the general formula VII



(VII),

where B has the above meanings, R^1 and R^2 are identical or

different and are each methyl or phenyl, and n is zero or one, and, if desired, the resulting compound is converted to its salts with physiologically tolerated or plant-tolerated acids.

If Me is hydrogen, reaction a) is carried out in the presence or absence of a solvent or diluent, with or without the addition of an inorganic or organic base or of a reaction accelerator, at from 10 to 120°C. Preferred solvents or diluents include ketones, eg. acetone, methyl ethyl ketone and cyclohexanone, nitriles, eg. acetonitrile, esters, eg. ethyl acetate, ethers, eg. diethyl ether, tetrahydrofuran and dioxane, sulfoxides, eg. dimethylsulfoxide, amides, eg. dimethylformamide, dimethylacetamide and N-methylpyrrolidone, and sulfolane, as well as mixtures of these.

Examples of suitable bases, which, if appropriate, may also be used as acid acceptors in the reaction, are alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide and potassium hydroxide, alkali metal carbonates, such as sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate, an excess of the 1,2,4-triazole, pyridine and 4-dimethylaminopyridine. However, it is also possible to use another conventional base.

Preferred reaction accelerators are metal halides, eg. sodium iodide or potassium iodide, quaternary ammonium salts, eg. tetrabutylammonium chloride, bromide or iodide or benzyl triethylammonium chloride or bromide, and crown ethers, eg. 12-crown-4, 15-crown-5,

18-crown-6, dibenzo-18-crown-6 or dicyclohexano-18-crown-6.

The reaction is carried out in general at from 20 to 150°C, under atmospheric or superatmospheric pressure, either continuously or batchwise.

If Me is a metal atom, reaction a) is carried out in the presence or absence of a solvent or diluent and with or without the addition of a strong inorganic or organic base, at from -10 to 120°C. Preferred solvents or diluents include amides, eg. dimethylformamide, diethylformamide, dimethylacetamide, diethylacetamide, N-methylpyrrolidone and hexamethylphosphorotriamide, sulfoxides, eg. dimethylsulfoxide, and sulfolane.

Examples of suitable bases, which, if appropriate, may also be used as acid acceptors in the reaction, are alkali metal hydrides, such as lithium hydride, sodium hydride and potassium hydride, alkali metal amides, such as sodium amide and potassium amide, and sodium tert.-butoxide, potassium tert.-butoxide, lithium-triphenylmethyl, sodium-triphenylmethyl, potassium-triphenylmethyl, naphthalene-lithium, naphthalene-sodium and naphthalene-potassium.

Suitable diluents for reaction b) are polar organic solvents such as nitriles, eg. acetonitrile, sulfoxides, eg. dimethylsulfoxide, formamides, eg. dimethylformamide, ketones, eg. acetone, ethers, eg. diethyl ether or tetrahydrofuran, and in particular chlorohydrocarbons, eg. methylene chloride or chloroform.

The reaction is carried out in general at from 0

to 100°C, preferably from 20 to 80°C. Where a solvent is used, the reaction is advantageously carried out at the boiling point of the particular solvent.

In carrying out process b), about 1 mole of carbonyl-bis-1-(1,2,4-triazole) or carbonyl-bis-1-imidazole, or 1 mole of sulfonyl-bis-1-(1,2,4-triazole) or sulfonyl-bis-1-imidazole, is preferably employed per mole of the compound of the formula II where L is OH, or the sulfonyl-bis-1-(1,2,4-triazole) or sulfonyl-bis-1-imidazole is produced in situ. To isolate the compounds of the formula I, the solvent is distilled off, the residue is taken up in an organic solvent, and the solution is washed with water.

The novel starting compounds II are obtained by epoxidizing the corresponding olefins IX:

$$L-CH_2-CA=CH-B \qquad (IX)$$

(cf. G. Dittus in Houben-Weyl-Müller, Methoden der organischen Chemie, Georg Thieme Verlag, Stuttgart, 1965, Volume VI, 3, page 385 et seq.).

The compound IX is prepared by halogenating or oxidizing an olefin of the formula X

$$H_3C-CA=CH-B \qquad (X)$$

at the allyl position, by a conventional method.

Suitable halogenating reagents are N-chlorosuccinimide and N-bromosuccinimide in halohydrocarbons, such as carbon tetrachloride, trichloroethane or methylene chloride, halogenation being carried out at from 20 to 100°C. Allyl oxidation is carried out using a perester, such as tert.-butyl perbenzoate or tert.-butyl

peracetate, in the presence of a heavy metal salt, eg. copper(I) chloride or copper(I) bromide, in an inert solvent at from 10 to 100°C.

The resulting allyl halide or alcohol IX is then converted to the corresponding epoxide II where L is halogen or OH. To do this, IX is oxidized with a peroxycarboxylic acid, eg. perbenzoic acid, 3-chloroperbenzoic acid, 4-nitroperbenzoic acid, monoperphthalic acid, peracetic acid, perpropionic acid, permaleic acid, monopersuccinic acid, perpelargonic acid or trifluoroperacetic acid, in an inert solvent, preferably a chlorohydrocarbon, eg. methylene chloride, chloroform, carbon tetrachloride or dichloroethane, or if appropriate even in acetic acid, ethyl acetate, acetone or dimethylformamide, in the presence or absence of a buffer, eg. sodium acetate, sodium carbonate, sodium bicarbonate, disodium hydrogen phosphate or Triton* B. The reaction is carried out at from 10 to 100°C, and, if necessary, is catalyzed, for example with iodine or sodium tungstate or by means of light. Oxidation may also be carried out using an alkaline solution of hydrogen peroxide (about 30% strength) in methanol, ethanol, acetone or acetonitrile at from 25 to 30°C, or an alkyl hydroperoxide, eg. tert.-butyl hydroperoxide, with the addition of a catalyst, eg. sodium tungstate, pertungstic acid, molybdenum hexacarbonyl or vanadyl acetylacetonate. Some of the above oxidizing agents can be produced in situ.

While the resulting epoxy halide II, where L is halogen, can be directly reacted further according to

* Trademark

process a), the corresponding epoxy alcohol II, where L is OH, is reacted with a compound of the formula IV according to process b), or is converted to a reactive ester, which is then reacted with a compound III according to process a).

The ester which is reacted with III is prepared by a conventional method (Houben-Weyl-Müller, Methoden der organischen Chemie, Georg Thieme Verlag, Stuttgart, 1955, Volume 9, pages 388, 663 and 671). Examples of such esters are methanesulfonates, trifluoromethanesulfonates, 2,2,2-trifluoromethanesulfonates, nonafluorobutanesulfonates, 4-methylbenzenesulfonates, 4-bromobenzenesulfonates, 4-nitrobenzenesulfonates and benzenesulfonates.

The compounds X, some of which are unknown, can be prepared by a conventional olefin synthesis (Houben-Weyl-Müller, Methoden der organischen Chemie, Georg Thieme Verlag, Stuttgart, 1972, Volume V, 1b).

Process c) is carried out by a procedure similar to the epoxidation of the compounds IX.

Some of the starting compounds V are known (German Laid-Open Application DOS 2,549,798). Those which are not known can be prepared by a method described in that publication.

In process d), according to the invention, a known azolyl ketone (for example, one which is disclosed in German Laid-Open Application DOS 2,063,857) of the formula VI is reacted with a sulfur derivative of the formula VII.

The alkylidenesulfuranes VII (where n is 0) and the oxysulfuranes VII (where n is 1) are prepared in situ by a conventional method (for example as described by H. O. House in Modern Synthetic Reactions, 2nd Edition, W. A. Benjamin, Menlo Park 1972, page 712 et seq.). A compound VII is reacted with an azolyl ketone VI in an inert solvent, preferably an ether, eg. diethyl ether, tetrahydrofuran or a mixture of these, or in a hydrocarbon, eg. pentane, hexane or petroleum ether, at from -78 to 30°C.

The resulting compound of the formula I is isolated by a conventional method, if necessary purified, and if desired reacted with an acid to give a salt.

Surprisingly, the azole derivatives according to the invention exhibit good antibacterial and antimycotic in vitro activity, as well as better therapeutically useful in vivo activity, in particular against dermatophytes and Candida, than conventional formulations. The active compounds according to the invention thus represent a valuable enrichment of the art.

The action against dermatophytes, bacteria and protozoa can be demonstrated by a method as described, for example, by P. Klein in Bakteriologische Grundlagen der chemotherapeutischen Laboratoriumspraxis, Springer-Verlag Berlin, 1957. The action against yeasts, which is surprising, was demonstrated in the pseudomycelium and mycelium phase tests with Candida albicans (cf. German Laid-Open Application DOS 3,010,093). The minimum inhibitory concentration (MIC) reached in the agar

dilution test was determined. The results are summarized in Table 1.

TABLE 1

Antimicrobial in vitro activity of the novel compounds

Substance of Example No.	Minimum inhibitory concentration (MIC) µg/ml Epid. flocc. 157	Microsp. ferrug. 5	Trichoph. ment. 21	Cand. alb. H	Cand. alb. M	Abs. corym. 1	Aps.fum. 2	Mucor pus. 6	Staph. sur. SG 511	Strept. faec. 8043	E.coli muta-flor	Trichom. vag.	Entamoeb hist.
6	0.125	0.0625	0.125	32	< 0.0039	8	0.0625	4	16	16	> 128	> 16	-
7	1	0.25	1	16	0.0156	1	4	2	16	16	> 128	> 16	-
9	1	0.25	1	> 1	< 0.125	4	16	2	128	128	> 128	> 16	-
1	0.5	0.125	0.5	16	< 0.0039	0.5	1	1	16	128	> 128	> 16	-
3	4	2	8	> 128	< 0.125	2	> 128	1	32	> 128	> 128	> 16	> 1
18	0.25	0.25	0.5	> 16	0.125	32	0.5	16	4	2	> 128	> 16	> 1
21	16	8	16	2	1	16	> 128	8	8	2	> 128	> 16	> 1
47	1	0.25	1	64	0.0156	2	16	2	8	4	> 128	> 16	> 1
29	2	2	2	128	0.25	8	16	4	16	4	> 128	> 16	> 1
30	8	2	8	64	2	16	> 128	8	> 128	> 128	> 128	> 16	> 1

In the guinea-pig trichophytosis model (Trichophyton mentagrophytes; cf. Heffter-Heubner: Handbuch d. exp. Pharmakologie, Vol. XVI/IIA), too, the novel compounds, when applied externally, exhibit a better action than comparative substances.

The novel substances are also active when administered orally, as can be shown from the treatment of experimental candidosis in the mouse. For this purpose, groups of 10 mice weighing about 20 g each were pretreated for 2 days, each mouse receiving 50 mg/kg of hydrocortisone intramuscularly, in order to ensure that they had been infected. The mice were then each infected intravenously with 500,000 Candida albicans germs, after which they each received, twice daily, 100 mg/kg of the substances to be tested, this dose being administered orally over a period of 4 days.

In addition to the infected group and the untreated control group, further groups were each treated with a reference substance for comparison. As a result, the test substances had better DC_{50} values than the reference substances.

In the experimental vaginitis model with Candida albicans in the rat, complete elimination of the infection was achieved after oral administration or local treatment using low therapeutic doses of the test substances.

The novel compounds are therefore particularly useful for the treatment of fungal infections in humans and animals by oral administration or external application.

Examples of fields of indication in humans and animals are dermatomycoses, dermatophytoses and systemmycoses, in particular those caused by dermatophytes, eg. species of the genera Epidermophyton, Microsporum and Trichophyton, yeasts, eg. species of the genera Candida, and molds, eg. species of the genera Aspergillus, Mucor and Absidia.

The compounds can be used alone or together with other conventional active compounds, in particular antibiotics.

The chemotherapeutic agents or formulations are prepared in a conventional manner, in particular by mixing an appropriate dose with the conventional solid, semi-solid or liquid carriers or diluents and the conventional pharmaceutical auxiliaries, in accordance with the desired route of administration (cf. H. Sucker et al., Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978).

Examples of suitable formulations are tablets, coated tablets, capsules, pills, aqueous solutions, suspensions and emulsions, and, if appropriate, sterile injectable solutions, non-aqueous emulsions, suspensions and solutions, ointments, creams, pastes, lotions, etc.

The therapeutically active compound is preferably present in the pharmaceutical formulation in a concentration of from 0.5 to 90% by weight, based on the total mixture.

To achieve the desired results in the case of oral administration either in human or in veterinary

medicine, the active compound or compounds can be administered in general in amounts of from about 1.0 to about 10.0, preferably from 2 to 6, mg/kg of body weight per day, preferably in the form of several single doses. However, it may be necessary to deviate from the stated doses, and to do this as a function of the nature and severity of the disorder, the type of formulation and the route of administration of the drug, as well as the period or interval between administrations. Thus, it may be sufficient in some cases to use less than the above-mentioned amount of active compound, while in other cases the above amount of active compound has to be exceeded.

The Examples which follow illustrate the invention.

I. Preparation of the starting materials

EXAMPLE A

63.6 g of potassium tert.-butylate in 300 ml of dry methanol were introduced into a solution of 229 g of 2,4-dichlorobenzyltriphenylphosphonium chloride in 800 ml of dry methanol at 10°C, and 77.2 g of 4-chloroacetophenone were added after half an hour. The reaction solution was refluxed for 3 hours and then cooled to room temperature, the precipitated salt was filtered off, the filtrate was evaporated down under reduced pressure, triphenylphosphine oxide was separated off from the residue by digesting the latter with petroleum ether at from 50 to 70°C, and the solution was evaporated down under reduced pressure.

The residue was taken up in 1 liter of carbon

tetrachloride, and the solution was refluxed with 81.7 g of N-bromosuccinimide and 4 g of 2,2'-azoisobutyrodinitrile. When the reaction was complete, the succinimide was filtered off, the filtrate was evaporated down under reduced pressure and the residue was recrystallized from methanol to give 73.4 g (38.8%) of Z-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-3-bromoprop-1-ene of melting point 128°C.

EXAMPLE B

118 g of 2,4-dichlorobenzyl chloride were added dropwise to 14.6 g of magnesium turnings in 400 ml of dry diethyl ether, at the boil. When the reaction was complete, 77.3 g of 4-chloroacetophenone in 400 ml of dry diethyl ether were added, and decomposition was then effected with aqueous ammonium chloride solution. The organic phase was separated off, washed neutral, dried over sodium sulfate and evaporated down under reduced pressure, the residue was taken up in 1 liter of toluene and the solution was refluxed with 4 g of 4-methylbenzenesulfonic acid, in a water separator. When dehydration was complete, the toluene phase was washed with sodium carbonate solution and water and dried over sodium sulfate, the solvent was evaporated off and the residue was recrystallized from methanol to give 107 g (71.9%) of E-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-prop-1-ene of melting point 84 - 85°C.

EXAMPLE C

104 g of E-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-prop-1-ene, 62.3 g of N-bromosuccinimide and 5 g

of 2,2'-azoisobutyrodinitrile in 1 liter of carbon tetrachloride were refluxed, the precipitated succinimide was filtered off, the filtrate was evaporated down under reduced pressure and the residue was treated with methanol to give 91.5 g (69.4%) of Z-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-3-bromoprop-1-ene of melting point 128°C.

EXAMPLE D

58.9 g of Z-1-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-3-bromoprop-1-ene (cf. Example A) and 52.3 g of 3-chloroperoxybenzoic acid in 590 ml of chloroform were refluxed. When the reaction was complete, the chloroform phase was washed acid-free with aqueous sodium bicarbonate solution and water, dried over sodium sulfate and evaporated down under reduced pressure, and the residue was recrystallized from methanol to give two fractions:

1. 41.3 g (70.2%) of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer A) of melting point 98 - 99°C and
2. 12 g (20.4%) of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer B) of melting point 93 - 95°C.

II. Preparation of the end products

EXAMPLE 1

A solution of 10 g of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer A, cf. Example D) in 50 ml of N,N-dimethylformamide was added dropwise, at 100°C, to a melt which was obtained from 15.6 g of imidazole and 1.37 g of sodium methylate and

from which the liberated methanol had been distilled off beforehand. After 8 hours, the reaction solution was poured onto water, and the mixture was extracted with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate and evaporated down under reduced pressure, and the residue was chromatographed over a silica gel column with methylene chloride/methanol (100 : 2). The pure fractions were evaporated down, and recrystallized from diisopropyl ether to give 4.6 g (47.5%) of 2-(1H-imidazol-1-ylmethyl)-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer A) of melting point 102 - 103°C.

EXAMPLE 2

6.2 g of imidazole and 1.3 g of sodium hydride (as a 50% strength dispersion in mineral oil) in 50 ml of N,N-dimethylformamide were initially taken, and a solution of 12 g of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer B, cf. Example D) and 5 g of potassium iodide in 50 ml of N,N-dimethylformamide was added at room temperature. After 8 hours, the reaction solution was poured onto water, and the mixture was extracted with ethyl acetate. The organic phase was washed with water and dried over sodium sulfate, the solvent was evaporated off under reduced pressure and the residue was recrystallized from diisopropyl ether to give 9.4 g (82.5%) of 2-(1H-imidazol-1-ylmethyl)-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer B) of melting point 109°C.

EXAMPLE 3

20.9 g of 1,2,4-triazole and 4.4 g of sodium hydride (as a 50% strength dispersion in mineral oil) in 150 ml of N,N-dimethylformamide were initially taken, and a solution of 39.2 g of 2-bromomethyl-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer A, cf. Example D) and 16.6 g of potassium iodide in 150 ml of N,N-dimethylformamide was added at room temperature. After 8 hours, the mixture was worked up as described in Example 2, and the product was recrystallized from diisopropyl ether to give 31 g (81.9%) of 2-(1,2,4-triazol-1-ylmethyl)-2-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-oxirane (isomer A) of melting point 119°C.

Some of the compounds listed in Table I were prepared by a procedure similar to that described in Example 1 or 2. The remaining compounds in the table can also be prepared as described in these Examples.

TABLE

Example No.	A	B	Z	Diastereomer	Mp.[°C]
4	4-Br-C_6H_4	C_6H_5	CH	A	152-153
5	4-Br-C_6H_4	4-Cl-C_6H_4	CH	A	143-144
6	C_6H_5	2,4-Cl_2-C_6H_3	CH	A	103
7	4-Br-C_6H_4	2,4-Cl_2-C_6H_3	CH	A	107-108
8	2,4-Cl_2-C_6H_3	4-Cl-C_6H_4	CH	A	135
9	4-Cl-C_6H_4	C_6H_5	CH	A	138
10	4-Br-C_6H_4	2,4-Cl_2-C_6H_3	N	A	133-134
11	CH_3	2,4-Cl_2-C_6H_3	CH	B	113-117.5
12	CH_3	2,4-Cl_2-C_6H_3	CH	A	98-104
13	$C(CH_3)_3$	4-Cl-C_6H_4	N	A	79- 80
14	$C(CH_3)_3$	4-Cl-C_6H_4	CH	A x HCl	214-216
15	$C(CH_3)_3$	C_6H_5	N	A x HCl	148
16	$C(CH_3)_3$	C_6H_5	CH	A	75
17	$C(CH_3)_3$	2,4-Cl_2-C_6H_3	N	A	124
18	$C(CH_3)_3$	2,4-Cl_2-C_6H_3	CH	A	95
19	4-Cl-C_6H_4	4-$C(CH_3)_3$-C_6H_4	CH	B	160-162
20	4-Cl-C_6H_4	4-$C(CH_3)_3$-C_6H_4	N	A	176-177

Example No.	A	B	Z	Diastereomer	Mp.[°C]
21	2.4-Cl_2-C_6H_3	4-$C(CH_3)_3$-C_6H_4	CH	A	132-134
22	CH_3	2,4-Cl_2-C_6H_3	N	A	105-108
23	CH_3	2,4-Cl_2-C_6H_3	N	B	80- 85
24	CH_3	2,4-Cl_2-C_6H_3	N	A:B = 1:1	70- 81
25	4-$C(CH_3)_3$-C_6H_4	4-Cl-C_6H_4	CH	A	100-152
26	4-$C(CH_3)_3$-C_6H_4	4-Cl-C_6H_4	N	A	105-107
27	4-$C(CH_3)_3$-C_6H_4	2,4-Cl_2-C_6H_3	CH	A	101-113
28	4-$C(CH_3)_3$-C_6H_4	2,4-Cl_2-C_6H_3	N	A	108-111
29	4-Cl-C_6H_4	3-OCH_3-C_6H_4	CH	A x HCl	173
30	4-Cl-C_6H_4	3-OCH_3-C_6H_4	N	A	77
31	C_6H_5	2,4-Cl_2-C_6H_3	N	A	159-161
32	4-Cl-C_6H_4	3-CF_3-C_6H_4	CH	A	101-104
33	4-Cl-C_6H_4	3-CF_3-C_6H_4	N	A	107-109
34	C_6H_5	3-CF_3-C_6H_4	CH	A	77- 78.5
35	C_6H_5	3-CF_3-C_6H_4	N	A x HCl	131-133
36	C_6H_5	C_6H_5	CH	A	108-110
37	4-Cl-C_6H_4	4-F-C_6H_4	CH	A	130-132
38	C_6H_5	4-Cl-C_6H_4	CH	A	105-106
39	C_6H_5	C_6H_5	N	A	116-118
40	C_6H_5	4-Cl-C_6H_4	N	A	114-115

Example No.	A	B	Z	Diastereomer	Mp.[°C]
41	4-Cl-C_6H_4	C_6H_5	N	A	106-110
42	4-C_6H_5-C_6H_4	4-Cl-C_6H_4	N	A	163-165
43	4-Br-C_6H_4	C_6H_5	N	A	115-120
44	4-Br-C_6H_4	4-Cl-C_6H_4	N	A	115-120
45	4-Cl-C_6H_4	4-F-C_6H_4	N	A	112-117
46	4-Cl-C_6H_4	4-Br-C_6H_4	N	A	115-119
47	4-Cl-C_6H_4	4-Br-C_6H_4	CH	A	114-116
48	4-Cl-C_6H_4	4-Br-C_6H_4	CH	B	179-181
49	2,4-Cl_2-C_6H_3	4-Br-C_6H_4	CH	A	135-139
50	4-Cl-C_6H_4	4-F-C_6H_4	N	B	219-223
51	4-Cl-C_6H_4	4-Br-C_6H_4	N	B	210-213
52	2,4-Cl_2-C_6H_3	4-Br-C_6H_4	N	A	108-110
53	2,4-Cl_2-C_6H_3	C_6H_5	CH	A	
54	2,4-Cl_2-C_6H_3	C_6H_5	CH	B	
55	2,4-Cl_2-C_6H_3	C_6H_5	N	A	
56	2,4-Cl_2-C_6H_3	C_6H_5	N	B	
57	4-(SO_2-C_6H_5)-C_6H_4	4-Cl-C_6H_4	CH	A	
58	4-(SO_2-C_6H_5)-C_6H_4	4-Cl-C_6H_4	CH	B	
59	4-(SO_2-C_6H_5)-C_6H_4	4-Cl-C_6H_4	N	A	
60	4-(SO_2-C_6H_5)-C_6H_4	4-Cl-C_6H_4	N	B	

Example No.	A	B	Z	Diastereomer	Mp.[°C]
61	2,4-Cl_2-C_6H_3	4-Cl-C_6H_4	N	A	
62	4-C_6H_5-C_6H_4	4-Cl-C_6H_4	CH		
63	2-Cl-C_6H_4	4-Cl-C_6H_4	CH		
64	2-Cl-C_6H_4	4-Cl-C_6H_4	N		
65	4-Cl-C_6H_4	3-Cl-C_6H_4	CH		
66	4-Cl-C_6H_4	3-Cl-C_6H_4	N		
67	C_6H_5	3,4-Cl_2-C_6H_3	CH		
68	C_6H_5	3,4-Cl_2-C_6H_3	N		
69	3,5-Cl_2-C_6H_3	4-Cl-C_6H_4	CH		
70	3,5-Cl_2-C_6H_3	4-Cl-C_6H_4	N		
71	2-OCH_3-C_6H_4	2,4-Cl_2-C_6H_3	CH		
72	2-OCH_3-C_6H_4	2,4-Cl_2-C_6H_3	N		
73	3,4-(O-CH_2-O)-C_6H_3	4-Br-C_6H_4	CH		
74	3,4-(O-CH_2-O)-C_6H_3	4-Br-C_6H_4	N		
75	4-O-$C(CH_3)_3$-C_6H_4	2,4-Cl_2-C_6H_3	CH		
76	4-O-$C(CH_3)_3$-C_6H_4	2,4-Cl_2-C_6H_3	N		
77	4-CH_3-C_6H_4	C_6H_5	CH		
78	4-CH_3-C_6H_4	C_6H_5	N		
79	4-(O-C_6H_5)-C_6H_4	4-Br-C_6H_4	CH		
80	4-(O-C_6H_5)-C_6H_4	4-Br-C_6H_4	N		

Example No.	A	B	Z	Diastereomer	mp.[°C]
81	C_6H_5	$4\text{-}NO_2\text{-}C_6H_4$	CH		
82	C_6H_5	$4\text{-}NO_2\text{-}C_6H_4$	N		
83	$2\text{-}C_{10}H_7$	$2,4\text{-}Cl_2\text{-}C_6H_3$	CH		
84	$2\text{-}C_{10}H_7$	$2,4\text{-}Cl_2\text{-}C_6H_3$	N		
85	$4\text{-}Cl\text{-}C_6H_4$	$1\text{-}C_{10}H_7$	CH		
86	$4\text{-}Cl\text{-}C_6H_4$	$1\text{-}C_{10}H_7$	N		
87	$4\text{-}Cl\text{-}C_6H_4$	$4\text{-}Cl\text{-}C_6H_4$	CH		
88	$4\text{-}Cl\text{-}C_6H_4$	$4\text{-}Cl\text{-}C_6H_4$	N		
89	$4\text{-}Br\text{-}C_6H_4$ (Salt with 1/2 Mol $CuCl_2$)	C_6H_5	CH	A	198-200

Examples of pharmaceutical formulations:

EXAMPLE A

Tablet containing 250 mg of active compound

Composition for 1,000 tablets:

Active compound of Example No. 3	250 g
Potato starch	100 g
Lactose	50 g
Gelatine solution (4% strength)	45 g
Talc	10 g

Preparation:

The finely powdered active compound, potato starch and lactose are mixed, the mixture is moistened thoroughly with about 45 g of 4% strength gelatine solution and then granulated to give fine particles, and the granules are dried. The dry granules are sieved and then mixed with 10 g of talc, and the mixture is pressed in a rotary tableting machine to give tablets. These are introduced into polypropylene containers which are closed tightly.

EXAMPLE B

Cream containing 1% of active compound

Active compound of Example No. 3	1.0 g
Glycerol monostearate	10.0 g
Cetyl alcohol	4.0 g
Polyethylene glycol-400 stearate	10.0 g
Polyethylene glycol sorbitan monostearate	10.0 g
Propylene glycol	6.0 g
Methyl p-hydroxybenzoate	0.2 g
Deionized water, to make up to	100.0 g

Preparation:

The very finely powdered active compound is suspended in propylene glycol, and the suspension is stirred into a melt, at 65°C, comprising glycerol monostearate, cetyl alcohol, polyethylene glycol-400 stearate and polyethylene glycol sorbitan monostearate. A solution, at 70°C, of methyl p-hydroxybenzoate in water is emulsified in this mixture, the emulsion is cooled, and the resulting cream is homogenized in a colloid mill and then introduced into tubes.

EXAMPLE C

Powder containing 1% of active compound

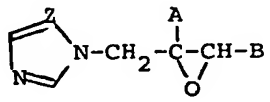
Active compound of Example No. 3	1.0 g
Zinc oxide	10.0 g
Magnesium oxide	10.0 g
Finely divided silicon dioxide	2.5 g
Magnesium stearate	1.0 g
Talc	74.5 g

Preparation:

The active compound is micronized in a jet mill employing air, and is then mixed with the other components to give a homogeneous mixture. This is forced through a sieve of No. 7 mesh size and then introduced into polyethylene containers with a perforated top.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

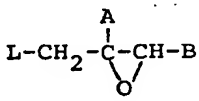
1. A process for the preparation of an azolylmethyloxirane of the formula I



(I),

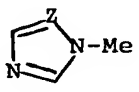
where A and B are identical or different and independently of one another are each alkyl of 1 to 4 carbon atoms, naphthyl, biphenyl or phenyl, and the phenyl radical can be substituted by halogen, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, phenoxy or phenylsulfonyl, and Z is CH or a nitrogen atom, and pharmaceutically acceptable acid addition salts thereof, wherein

a) a compound of the formula II



(II),

where A and B have the above meanings and L is a leaving group which can undergo nucleophilic substitution, is reacted with a compound of the formula III

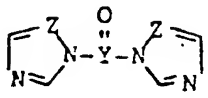


(III),

where Me is hydrogen or a metal atom and Z is CH or a

nitrogen atom, or

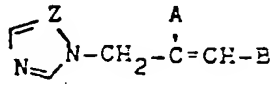
b) a compound of the formula II, where A and B have the above meanings and L is hydroxyl, is reacted with a compound of the formula IV



(IV),

where Z has the above meanings and Y is carbon or sulfur, or

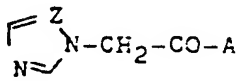
c) a compound of the formula V



(V),

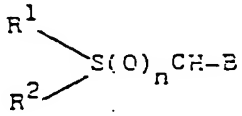
where Z, A and B have the above meanings, is epoxidized, or

d) a compound of the formula VI



(VI),

where Z and A have the above meanings, is reacted with a compound of the formula VII



(VII),

where B has the above meanings, R1 and R2 are identical or

different and are each methyl or phenyl, and n is zero or one, and, if desired, the resulting compound is converted to a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula I as defined in claim 1 and pharmaceutically acceptable acid addition salts thereof whenever obtained by a process as defined in claim 1 or an obvious chemical equivalent thereof.

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